
General Background Document: Aredia and Zometa

In 2003, the first published reports appeared in the literature of osteonecrosis of the jaw (ONJ) in patients with malignancy whose treatment regimens included intravenous bisphosphonates. In a high proportion of cases, there was an association with a recent dental procedure. These patients had no history of radiation therapy to the head and neck.

Pamidronate (Aredia) and zoledronic acid (Zometa) are potent intravenous bisphosphonates. Pamidronate injection is indicated, in conjunction with standard antineoplastic therapy, for the treatment of osteolytic metastases of breast cancer and osteolytic lesions of multiple myeloma, as well as hypercalcemia of malignancy (HCM) and Paget's Disease. Zoledronic acid injection is indicated for the treatment of HCM and for the treatment of patients with multiple myeloma and patients with documented metastases from solid tumors, in conjunction with standard antineoplastic therapy. Prostate cancer should have progressed after treatment with at least one hormonal therapy. Aredia received approval for HCM in 1991, for multiple myeloma in 1995, and for osteolytic bone metastases from breast cancer in 1998. Zometa was approved for HCM in August 2001 and for a broad bone metastasis indication in February 2002.

The Zometa package insert was updated in September 2003 and February 2004 to include information on osteonecrosis of the jaw in the adverse events section. The Aredia package insert was subsequently updated, as well. In August 2004, additional changes were made to the Precautions section of the Zometa label, followed by parallel changes to the Aredia label, regarding ONJ. Novartis issued a Dear Doctor letter in September 2004 regarding ONJ.

The purpose of bringing to ODAC the problem of ONJ in association with the intravenous bisphosphonates is to highlight a drug safety issue in oncology and stimulate discussion of how post-marketing safety issues in oncology should be addressed. Although there have been anecdotal reports of ONJ in association with oral bisphosphonates administered for osteoporosis, we wish to limit today's discussion to ONJ in association with Zometa and Aredia. There have been fewer reports of ONJ associated with the oral bisphosphonates, and risk-benefit considerations are different for patients with malignant as opposed to benign disease.

Below are excerpts from the approved product labeling for Zometa and Aredia that include information on osteonecrosis of the jaw in the PRECAUTIONS and ADVERSE REACTIONS sections of the package inserts.

- **PRECAUTIONS: Osteonecrosis of the Jaw**

Osteonecrosis of the jaw (ONJ) has been reported in patients with cancer receiving treatment regimens including bisphosphonates. Many of these patients were also receiving chemotherapy and corticosteroids. The majority of reported

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cases have been associated with dental procedures such as tooth extraction. Many had signs of local infection including osteomyelitis.

A dental examination with appropriate preventive dentistry should be considered prior to treatment with bisphosphonates in patients with concomitant risk factors (e.g. cancer, chemotherapy, corticosteroids, poor oral hygiene).

While on treatment, these patients should avoid invasive dental procedures if possible. For patients who develop ONJ while on bisphosphonate therapy, dental surgery may exacerbate the condition. For patients requiring dental procedures, there are no data available to suggest whether discontinuation of bisphosphonate treatment reduces the risk of ONJ. Clinical judgment of the treating physician should guide the management plan of each patient based on individual benefit/risk assessment.

• **Adverse Events: Post-Marketing Experience**

For Zometa:

Cases of osteonecrosis (primarily involving the jaws) have been reported in patients treated with bisphosphonates. The majority of the reported cases are in cancer patients attendant to a dental procedure. Osteonecrosis of the jaws has multiple well-documented risk factors including a diagnosis of cancer, concomitant therapies (e.g., chemotherapy, radiotherapy, corticosteroids) and co-morbid conditions (e.g., anemia, coagulopathies, infection, pre-existing oral disease). Although causality cannot be determined, it is prudent to avoid dental surgery as recovery may be prolonged. (See PRECAUTIONS.)

For Aredia:

Cases of osteonecrosis (primarily of the jaws) have been reported since market introduction. Osteonecrosis of the jaws has other well documented multiple risk factors. It is not possible to determine if these events are related to Aredia or other bisphosphonates, to concomitant drugs or other therapies (e.g., chemotherapy, radiotherapy, corticosteroid), to patient's underlying disease, or to other comorbid risk factors (e.g., anemia, infection, preexisting oral disease). (See PRECAUTIONS.)